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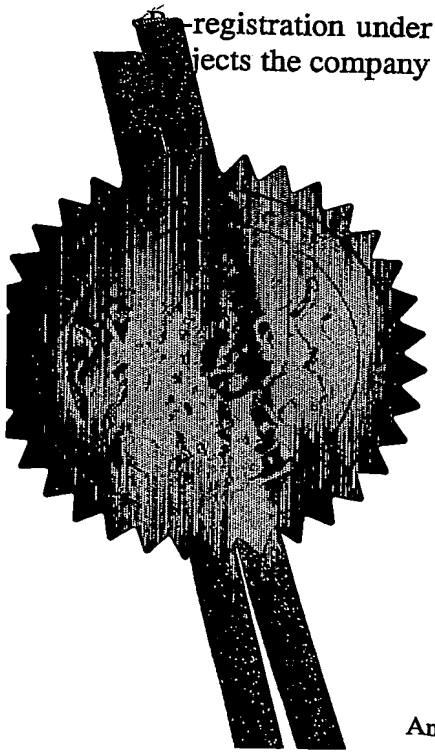

Signed R. Mahone

Dated 28 November 2003

14OCT03 E844270-1 D00245
P01/7700 0.00-0323976.1

Patents Form 1/77

Patents Act 1977
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THE PATENT OFFICE
13 OCT 2003
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The Patent Office

1/77

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office
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1.	Your reference	4-32540P2/NFI 8021
2.	Patent application number *(The Patent Office will fill in this part)*	0323976.1 13 OCT 2003
3.	Full name, address and postcode of the or of each applicant *(underline all surnames)*	NOVARTIS AG LICHTSTRASSE 35 4056 BASEL SWITZERLAND
	Patent ADP number *(if you know it)*	
	If the applicant is a corporate body, give the country/state of its incorporation	SWITZERLAND
4.	Title of invention	Organic Compounds
5.	Name of your agent *(If you have one)*	Craig McLean
	"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*	Novartis Pharmaceuticals UK Limited Patents and Trademarks Wimblehurst Road Horsham, West Sussex RH12 5AB
	Patents ADP number *(if you know it)*	07181522002

7125487005

6.	If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number	Country	Priority application number *(if you know it)*	Date of filing (day/month/year)

7.	If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application	Number of earlier application	Date of filing (day/month/year)

8.	Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:* *a) any applicant named in part 3 is not an inventor, or* *b) there is an inventor who is not named as an applicant, or* *c) any named applicant is a corporate body.* *(see note (d))*	Yes

Patents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	
Description	26
Claim(s)	3
Abstract	1
Drawing(s)	

10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application

Signature Date

Craig McLean 13th October 2003

12. Name and daytime telephone number of person to contact in the United Kingdom

Mr. Trevor Drew 01403 323069

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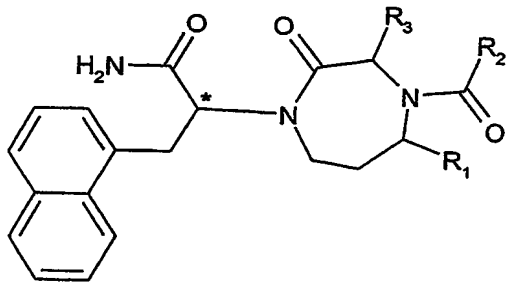
DUPLICATE

Organic compounds

The present invention relates to organic compounds, e.g. diazepanes. In one aspect the present invention provides a compound of formula



I

wherein

R_1 is (C_{1-4})alkyl,

R_2 is (C_{1-4})alkyl or $-(CH_2)_n-R_4$ wherein

n is 1, 2, 3 or 4 and

R_4 is unsubstituted or substituted

- phenyl or
- phenyl anellated with another ring system, which other ring system is a 5- or 6-membered heterocycle, having one to 4 heteroatoms, preferably 1 or 2, selected from N, O or S, preferably from N or O,

e.g. wherein substituents are selected from the group consisting of

- halogen,
- unsubstituted amino or amino substituted by one or two (C_{1-4})alkyl,
- cyano,
- (C_{1-4})alkoxy,
- (C_{1-6})haloalkyl and

R_3 is substituted phenyl, e.g. one or morefold, wherein the substituents are selected from the group consisting of

- halogen,
- (C_{1-6})haloalkyl,
- unsubstituted or substituted phenyl, e.g. substituted by substitutents as indicated under R_4.

Phenyl anellated with another ring system includes e.g.

- benzo(1,3)dioxo-4-yl, benzo(1,3)dioxo-5-yl,
- quinolin-5-yl, quinolin-6-yl, quinolin-7-yl, quinolin-8-yl.

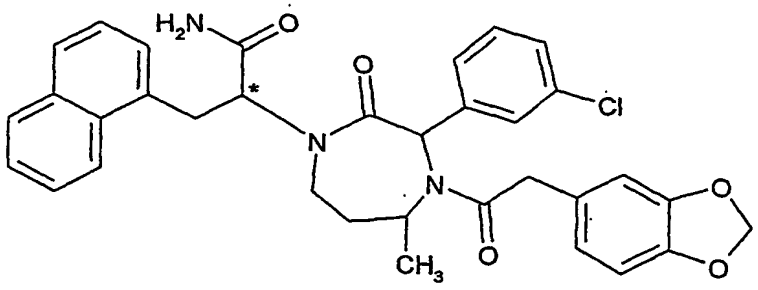
If not otherwise defined herein

- alkyl is (C_{1-4})alkyl and may be linear or branched
- alkyl includes unsubstituted or substituted alkyl, e.g. substituted by groups which are conventional in organic chemistry, e.g. halogen, OH, (C_{1-6})haloalkyl, e.g. (C_{1-4})haloalkyl such as CF_3, or NH_2,
- haloalkyl is (C_{1-6})haloalkyl, e.g. (C_{1-4})haloalkyl, wherein one or more halogen(s) is (are) present in the alkyl group, preferably $-CF_3$
- halogen includes F, Cl or Br.

In another aspect the present invention provides a compound of formula I, wherein

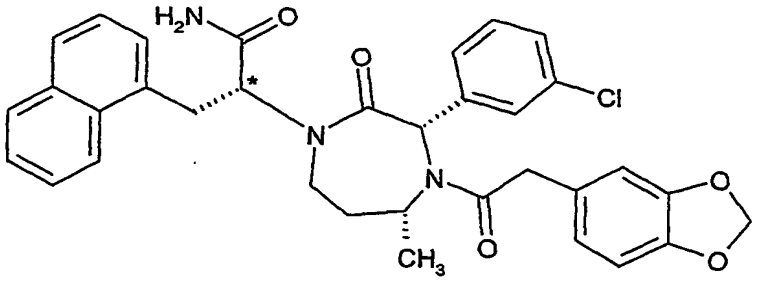
- R_1 is methyl,
- R_2 is methyl or $-CH_2-R_4$ wherein R_4 is phenyl, substituted phenyl, benzo(1,3)dioxo-4-yl, benzo(1,3)dioxo-5-yl, quinolin-5-yl, quinolin-6-yl, quinolin-7-yl, quinolin-8-yl, preferably R_4 is benzo(1,3)dioxo-5-yl,quinolin-6-yl, phenyl or phenyl substituted by one or more
  - halogen, e.g. chloro,
  - unsubstituted or substituted amino, e.g. (C_{1-4})dialkylamino, such as dimethylamino; carboxy(C_{1-4})alkylcarbonylamino, amino(C_{1-4})alkylcarbonylamino, (C_{1-6})alkoxycarbonyl-amino, such as tert.butoxycarbonylamino, (C_{2-4})alkylenecarbonylamino, such as allylcarbonylamino;
  - cyano,
  - (C_{1-4})alkoxy, such as methoxy,
  - (C_{1-4})haloalkyl, such as $-CF_3$, and
- R_3 is substituted phenyl, e.g. one or morefold, wherein the substituents are selected from the group consisting of
  - halogen, e.g. fluoro, chloro bromo,
  - (C_{1-4})haloalkyl, such as $-CF_3$,
  - unsubstituted phenyl.

In another aspect the present invention provides a compound of formula I which is a compound of formula



I_{PREF}

e.g. including the compound



I'_{PREF}

Compounds provided by the present invention, e.g. including compounds of formula I, I_{PREF} and I'_{PREF} are hereinafter designated as "compound(s) of (according to) the present invention". Each single substituent defined above in a compound of formula I may be per se a preferred substituent, independently of the other substituents defined.

A compound of the present invention includes a compound in any form, e.g. in free form, in the form of a salt, in the form of a solvate and in the form of a salt and in the form of a solvate. A compound of the present invention in free form may be converted into a corresponding compound in the form of a salt; and vice versa. A compound of the present invention in free form or in the form of a salt and in the form of a solvate may be converted into a corresponding compound in free form or in the form of a salt in unsolvated form; and vice versa.

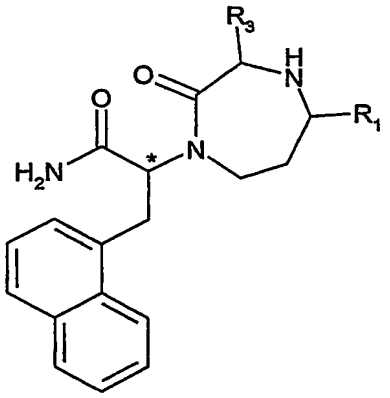
In another aspect the present invention provides a compound of the present invention in the form of a salt.

A salt of a compound of the present invention includes a pharmaceutically acceptable salt, e.g. including a metal salt or an acid addition salt. Metal salts include for example alkali or earth alkali; acid addition salts include salts of a compound of formula I with an acid, e.g. acetic acid, trifluoroacetic acid, hydrochloric acid; preferably trifluoroacetic acid.

A compound of of the present invention may exist in the form of isomers and mixtures thereof; e.g. optical isomers, diastereoisomers, cis trans conformers. A compound of the present invention may e.g. contain asymmetric carbon atoms and may thus exist in the form of diastereoisomeres and mixtures thereof, e.g. racemates. For example the groups R_1, R_3 and the group naphthylmethyl in position * in a compound of formula I may be in the (R)- and/or in the (S)-configuration, e.g. including mixtures therof. Isomeric mixtures may be separated as appropriate, e.g. according, such as analogously, to a method as conventional, to obtain pure isomers. The present invention includes a compound of the present invention in any isomeric form and in any isomeric mixture.
Similar considerations apply in relation to starting materials exhibiting isomeric features, e.g. analogously as indicated above.

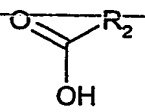
Any compound described herein, e.g. a compound of the present invention, may be prepared as appropriate, e.g. according to a method as conventional or, e.g. as specified herein. Starting materials are known or may be prepared according to, e.g. analogously, to a method as conventional or as disclosed herein.

In another aspect the present invention provides a process for the preparation of a compound of the present invention comprising
A) reacting a compound of formula



II

wherein R_1 and R_3 are as defined above, with a compound of formula

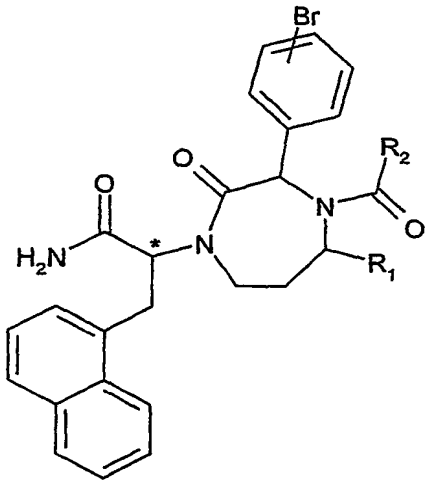


III

e.g. in a protected form,
e.g. in the presence of a
- condensing agent, e.g. a carbodiimide
- an amine, e.g. dimethylaminopyridine,

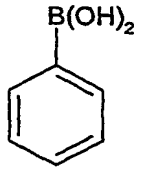
in organic solvent, e.g. polar organic solvent, such as N,N-dimethylformamide, optionally deprotecting, and optionally further reacting, to obtain a compound of formula I, or

B) reacting a compound of formula



IV

wherein R_1 and R_3 are as defined above, with an optionally substituted compound of formula



V

to obtain a compound of formula I wherein R_3 is phenyl substituted by optionally substituted phenyl,
and isolating a compound of formula I obtained from the reaction mixture.

An optionally protected group of formula III e.g. includes phenyl substituted by an amine. Such amine may be protected by an appropriate protection group, e.g. including tert-butoxycarbonyl (Boc), which protecting group may be removed after reaction of a compound of formula II with a compound of formula III to obtain a free amine group. Further reacting e.g. includes alkylating such amine group, e.g. analogously to a method as conventional. Optionally in a compound of formula II or in a compound of formula III groups may be protected.

The compounds of the present invention exhibit valuable pharmacological properties, e.g. by mediating, such as inhibiting, the activity of LFA-1/ICAM-1, LFA-1/ICAM-2 or LFA-1/ICAM-3 interactions and thus mediating, e.g. inhibiting inflammation, e.g. as indicated in in vitro and in vivo tests herein and are therefore indicated for therapy. Therapy includes medical treatment and prophylactic treatment.

A. **In vitro**: Cell Free Assay

The assay determines the binding of soluble human ICAM-1 to immobilized human LFA-1. LFA-1 is purified from JY cells, a human lymphoblastoid B cell-line, by immunoaffinity chromatography analogously as described by Dustin *et al.*, J. Immunol. 148, 2654-2663, 1992. ICAM-1 mouse Cκ fusion protein (ICAM-1) is produced using the baculovirus system as described by Weitz-Schmidt *et al.*, Anal. Biochem. 238,184-190, 1996.

Purified LFA-1 is diluted 1:20 in phosphate buffered saline (PBS) containing 2 mM $MgCl_2$, pH 7.4 and coated onto microtitre plates (Nunc) at 37° for 3hours. Plates are blocked with 1% heat-treated bovine serum albumin in PBS for 2 hours at 37° followed by a washing step using PBS, 2mM $MgCl_2$, 1% fetal calf serum, pH 7.4 (assay buffer). Compounds of the present invention dissolved at 10 mM in DMSO are diluted in assay buffer and added to the plates. Biotinylated recombinant ICAM-1 in assay buffer (6 µg/ml) is added and allowed to bind at 37° for one hour. After incubation, wells are washed with assay buffer. Streptavidin-peroxidase diluted 1:5000 in assay buffer is added and incubated for 45 min at 37°. Plates are washed with assay buffer and 2,2'-azino-bis(3-ethylbenzothiazoline-6 sulfonic acid) diammonium salt substrate solution is added to each well. The reaction is stopped after 20 minutes and bound ICAM-1 is determined by measuring the optical density at 405 nm in a microplate reader.

In this assay the compounds of the present invention exhibit activity, e.g. the compounds of the present invention inhibit adhesion of LFA-1 to ICAM-1 with an $IC_{50} \leq 50$ µM, preferably 0.05 to 30 µM. Compounds of Examples 13 and 14 have an IC_{50} of 0.43 and 0.09 µM, respectively, in this assay.

B. In vivo

Bi) Murine Thioglycollate Induced Peritonitis

Thioglycolate is injected i.p. to mice and immediately thereafter the compound of the present invention which is to be tested is given s.c. The mice are killed after 4 hours, the peritoneal cavity is lavaged and the total number of neutrophils in the lavage fluid is determined.

In this assay the compounds of the present invention exhibit activity, e.g. the compounds of the present invention inhibit thioglycolate induced neutrophil migration when administered p.o., e.g. at a dose of from 0.001-50 mg/kg administrated either at the time of thioglycolate injection or 3 hours before.

Bii) Allergic Contact Dermatitis (ACD)

Groups of 8 female NMRI mice are sensitized on the shaved abdomen with 50 µl of oxazolone (Sigma, 2% in acetone) and challenged with 10 µl of 0.2 or 2.0% oxazolone on the inner surface of the right ear 7 days later. The low concentration of oxazolone for induction of the elicitation phase is used for testing compounds of the present invention on systemic activity whereas the high concentration is applied for systemic testing. The unchallenged left ears serve as normal controls and dermatitis is evaluated from the individual differences in pinnal weight, which is taken as a measure of increase in inflammatory swelling 24 h after the challenge. Dermatitis is evaluated in test- and for comparison in control groups. The test groups are treated with the test compounds either orally (twice, 2 h and immediately before challenge), subcutaneously (immediately before challenge) or topically (30 min after challenge at the site of elicitation of the ACD), the controls are treated similarly with the vehicles alone. For oral and subcutaneous administration the compounds are administered in an oil in H_2O emulsion, for topical administration the compounds are prepared in a mixture of ethanol, acetone and dimethylacetamide. The data of the test- and the vehicle-treated control groups are statistically analysed by ANOVA followed by Dunnet T-test (normal distribution or data) or by H and U-test, respectively. When administered p.o. at a dose of from 0.1 to 10 mg/kg, the compounds of the present invention inhibit the elicitation phase of allergic contact dermatitis. For example, compound of Example 14 has an inhibiting effect in this assay of 40% when administered p.o. at a dose of 2 x 0.03 mg/kg.

The compounds of the present invention are therefore useful in the treatment and/or prevention of diseases or disorders mediated by LFA-1/ICAM-1, LFA-1/ICAM-2 or LFA-1/ICAM-3 interactions e.g. including ischemia/reperfusion injury e.g. myocardial infarction, stroke, gut ischemia, renal failure or hemorrhage shock, acute or chronic rejection

of organ or tissue allo- or xenografts, cancer, infection diseases such as septic shock, adult respiratory distress syndrome, or traumatic shock. The compounds of the present invention are also useful in the treatment and/or prevention of acute or chronic inflammatory diseases or disorders or autoimmune diseases e.g. rheumatoid arthritis, osteoarthritis, systemic lupus erythematosus, hashimoto's thyroidis, multiple sclerosis, myasthenia gravis, diabetes type I and uveitis, asthma, inflammatory lung injury, inflammatory liver injury, inflammatory glomerular injury, cutaneous manifestations of immunologically-mediated disorders or illnesses, inflammatory and hyperproliferative skin diseases (such as psoriasis, atopic dermatitis, alopecia aerata, allergic contact dermatitis, irritant contact dermatitis and further eczematous dermatitises, seborrhoeic dermatitis, lichen planus, pemphigus, bullous pemphigoid, epidermolysis bullosa, urticaria, angioedemas, vasculitides, erythema multiforme, cutaneous eosinophilias, lupus erythematosus, acne, granuloma annulare, pyoderma gangrenosum, sun burns or toxic epidermal necrolysis), inflammatory bowel disease (IBD), Crohn's disease, ulcerative colitis, ophthalmic inflammatory diseases or immune-mediated conditions of the eye, such as auto-immune diseases, e.g. keratoplasty and chronic keratitis, allergic conditions, e.g. vernal conjunctivitis, inflammatory conditions and corneal transplants.

In a preferred aspect the compounds of the present invention are useful in the treatment and/or prevention of autoimmune diseases, e.g. rheumatoid arthritis, or of inflammatory diseases, e.g. psoriasis.

In a more preferred aspect the compounds of the present invention are useful in the treatment and/or prevention of rheumatoid arthritis.

For the above uses the required dosage will of course vary depending on the mode of administration, the particular condition to be treated and the effect desired. In general, satisfactory results are indicated to be obtained systemically at daily dosages of a compound of the present invention from about 0.1 to about 100 mg/kg body weight. An indicated daily dosage in the larger mammal, e.g. humans, is in the range from about 0.5 mg to about 500 mg, conveniently administered, for example, in divided doses up to four times a day or in retard form.

The compounds of the present invention may be administered systemically or topically, by any conventional route, in particular enterally, e.g. orally, e.g. in the form of tablets or capsules, topically, e.g. in the form of lotions, gels, ointments or creams, or in a nasal or a suppository form. Percutaneous administration via patches or other delivery systems may also be a possible route for prevention or treatment of above diseases.

For topical use, e.g. including administration to the eye, satisfactory results are obtained with local administration of a 0.5-10 %, such as 1-3% concentration of active substance several times daily, e.g. 2 to 5 times daily.

In another aspect the present invention provides a pharmaceutical composition comprising a compound of the present invention in association with at least one pharmaceutically acceptable excipient, e.g. including a carrier and/or diluent. Such compounds may be prepared according, e.g. analogously, to a method as conventional, e.g. by mixing a compound of the present invention with a pharmaceutically acceptable excipient, e.g. a carrier and/or diluent. Unit dosage forms for oral administration contain, for example, from about 0.1 mg to about 1000 mg, e.g. 0.5 mg to 500 mg, such as e.g. 1 mg to about 125 mg of a compound of the present invention.

The compounds of the present invention in the form of a salt exhibit the same order of activity as the compounds of the present invention in free form; optionally in the form of a solvate.

In another aspect the present invention provides:

- A method for preventing or treating disorders or diseases mediated by LFA-1/ICAM-1, LFA-1/ICAM-2 or LFA-1/ICAM-3 interactions, e.g. such as indicated above, in a subject in need of such treatment, which method comprises administering to said subject an effective amount of a compound of the present invention
- A method for preventing or treating acute or chronic inflammatory diseases or disorders or autoimmune diseases, e.g. as indicated above, e.g. autoimmune diseases e.g. rheumatoid arthritis, psoriasis or other inflammatory skin diseases, in a subject in need of such treatment, which method comprises administering to said subject an effective amount of a compound of the present invention
- A compound of of the present invention for use as a pharmaceutical

- A compound of of the present invention for use in the preparation of a pharmaceutical composition for use in a method for preventing or treating disorders or diseases as indicated above.

A compound of the present invention may be used for pharmaceutical treatment according to the present invention alone or in combination with at least one, e.g. one or more, other pharmaceutically active agents. Such other pharmaceutically active agents e.g. include compounds active in immunomodulating regimens or other anti-inflammatory agents, e.g. for the treatment or prevention of allo- or xenograft acute or chronic rejection or inflammatory or autoimmune disorders. For example, compounds of the present invention may be used in combination with cyclosporins, rapamycins or ascomycins, or their immunosuppressive analogs, e.g. cyclosporin A, cyclosporin G, FK-506, ASM 981, rapamycin, 40-O-(2-hydroxy)ethyl-rapamycin etc., corticosteroids, cyclophosphamide, azathioprene, methotrexate, FTY 720, leflunomide, mizoribine, mycophenolic acid, mycophenolate mofetil, 15-deoxyspergualine, immunosuppressive monoclonal antibodies, e.g., monoclonal antibodies to leukocyte receptors, e.g., MHC, CD2, CD3, CD4, CD7, CD25, CD28, B7, CD40, CD45, or CD58 or their ligands, or other immunomodulatory compounds, e.g. CTLA4Ig, or other adhesion molecule inhibitors, e.g. mAbs or low molecular weight inhibitors including Selectin antagonists and VLA-4 antagonists.

Combinations include fixed combinations, in which two or more pharmaceutically active agents are in the same formulation; kits, in which two or more pharmaceutically active agents in separate formulations are sold in the same package, e.g. with instructions for co-administration; and free combinations in which the pharmaceutically active agents are packaged separately, but instructions for simultaneous or sequential administration are given.

If the compounds of the present invention are administered in combination with other immunosuppressive/immunomodulatory or anti-inflammatory active agents, e.g.for preventing or treating acute or chronic rejection or inflammatory or autoimmune disorders as hereinabove specified, dosages of the co-administered immunosuppressant, immunomodulatory or anti-inflammatory compound will of course vary depending on the type of co-drug employed, e.g. whether it is a steroid or a cyclosporin, on the specific drug employed, on the condition being treated and so forth. In general comparable dosage ranges

as indicated for the co-administered immunosuppressant, immunomodulatory or anti-inflammmatory agent are appropriate.

In another aspect the present invention provides

- A method for preventing or treating disorders or diseases as indicated above comprising co-administrating, e.g. concomitantly or in sequence, a therapeutically effective amount of at least one compound of the present invention and at least one second pharmaceutically active agent, said pharmaceutically active agent being selected from the group consisting of immunosuppressants, immunomodulatory or anti-inflammatory active agents, e.g. such as indicated above.
- A therapeutic combination, e.g. a kit, for use in any method according to the present invention, comprising at least one compound of the present invention to be used concomitantly or in sequence with at least one immunosuppressant, immunomodulatory or anti-inflammatory active agent. The kit may comprise instructions for concomitant administration or administration in sequence.

In the following examples which illustrate the present invention all temperatures are given in degree centigrade. RT means room temperature.

The following ABBREVIATIONS are used:

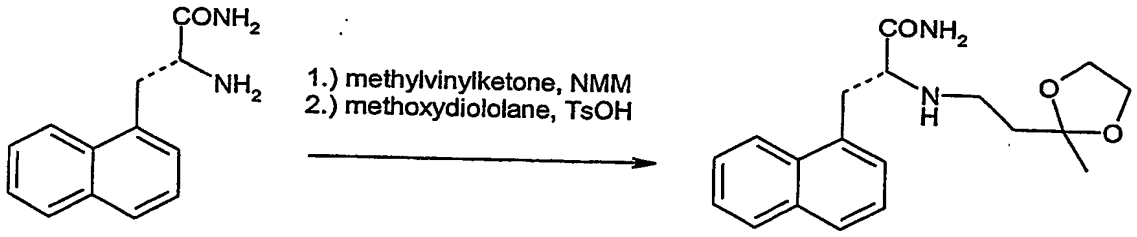
AcOH	acetic acid
Boc	tert.-butoxy-carbonyl
DBU	1,4-diaza-bucyclo[5.4.0]undec-7-en
DIEA	diisopropylethylamine
DIPCI	diisopropylcarbodiimide
DMAP	N,N-dimethyl-4-aminopyridin
DMF	N,N-dimethylformamide
EDC	N-ethyl-N`-(3-dimethylaminopropyl)-carbodiimide
EtAc	ethyl acetate
equiv.	equivalent
HOAt	1-hydroxy-7-azabenzotriazol
i-PrOH	isopropanol
MeOH	methanol

NMM	N-methyl-morpholine
THF	tetrahydrofuran
TFA	trifluoroacetic acid
TsOH	p-toluenesulfonic acid
Z	benzyloxycarbonyl

EXAMPLES

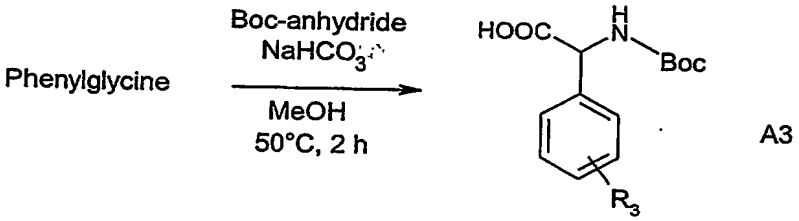
Procedure A:

a) Synthesis of a ketal intermediate



A1 A2

Naphthylalanine amide of formula A1 and 0.3 equiv. of NMM are dissolved in dioxan and 1.5 equiv. of methylvinylketone are added. The mixture obtained is stirred at RT for 15 hours and 5 equiv. of 2-methoxydioxolane and 1.5 equiv. of TsOH-monohydrate are added. The mixture obtained is stirred, diluted with EtAc, washed and dried. Solvent is evaporated and a ketal of formula A2 is obtained, which is used directly for further steps or can be purified before further use.



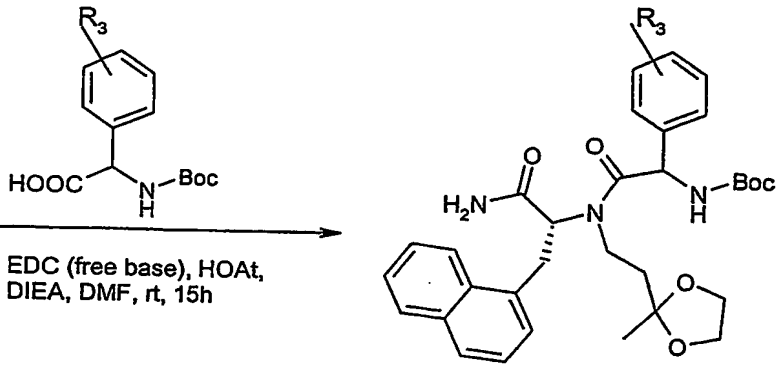
A3

b) Boc-protection of phenylglycines

Phenylglycine or substituted phenylglycine, wherein R_3 has the meaning as indicated above, is dissolved in MeOH, 2 equiv. of $NaHCO_3$ and 1.2 equiv. of Boc-anhydride are added and the suspension obtained is heated at 50° under stirring. Solvent is evaporated and H_2O and toluene are added. The phases obtained are separated and the organic phase is extracted with 1N NaOH. The pH of the aqueous phase obtained is adjusted to pH 3 and the mixture obtained is extracted with EtAc. The organic phase obtained is dried, solvent is evaporated and racemic Boc-phenylglycine is obtained.

c) Preparation of dipeptide derivatives

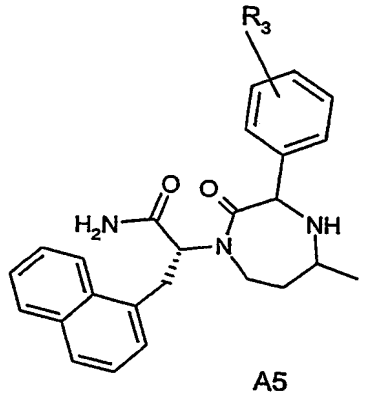
Compound of formula A2 → (EDC (free base), HOAt, DIEA, DMF, rt, 15h) → A4



1 equiv. of a compound of formula A2, 1.5 equiv. of racemic Boc-phenylglycine or substituted phenylglycine, wherein R_3 has the meaning as indicated above, and 0.12 equiv. of HOAt are dissolved in DMF and 1.5 equiv. of DIEA and 1.5 equiv. of EDC in free base form are added during 10 hours at RT. Solvent is evaporated, the evaporation residue obtained is diluted with EtAc and extracted with 1N HCl and 5% $NaHCO_3$ solution. The organic phase obtained is dried and solvent is evaporated. A compound of formula A4 is obtained in the form of a diastereoisomeric mixture.

d) Deprotection and reductive ring closure of diazepanes

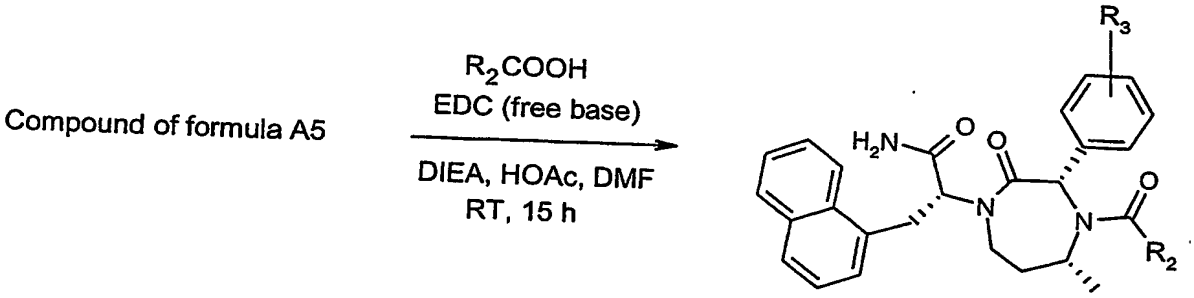
Compound of formula A4 → (1.) TFA/H_2O 9:1, 0°C, 2h; 2.) $NaCNBH_3$, MeOH/H_2O, NEt_3/AcOH Buffer pH=5, 0°C, 1h) → A5



The crude compound of formula A4 is dissolved in TFA/ H_2O at 0°. The reaction mixture obtained is stirred, quenched with H_2O and solvent is evaporated. A diastereoisomeric mixture of the deprotected compound of formula A4 is dissolved in MeOH/H_2O and the pH is adjusted to pH 5. 0.5 equiv. of a sodium cyanoborohydride solution in MeOH/H_2O is added at 0° and the mixture obtained is stirred. Solvent is evaporated, a residue obtained is diluted with EtAc and washed with 3.5M phosphate-buffer pH 4 and 5% $NaHCO_3$ solution. The

organic phase obtained is dried and solvent is evaporated. A compound of formula A5 wherein R_3 is as defined above is obtained.

e) Preparation of diazepane derivatives

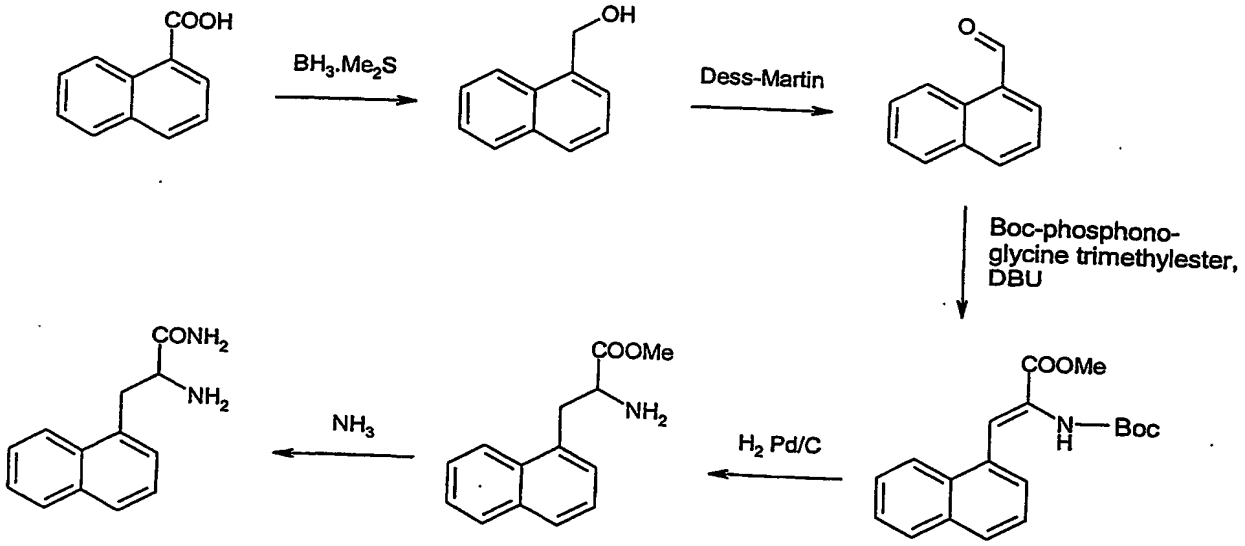


A6

A crude amine of formula A5 is treated with 1.7 equiv. of R_2COOH, 1.3 equiv. of DIEA and 0.2 equiv. of HOAt in DM. A reaction mixture obtained is heated to 35° and 1.7 equiv. of EDC in free base form are added and stirred for 15 hours at 35°. Solvent is evaporated, the evaporation residue obtained is diluted with EtAc and the mixture obtained is extracted. The organic phase obtained is dried and solvent is evaporated. A compound of formula A6 is obtained, which can be subjected to chromatography (e.g. silica gel, toluene/i-PrOH).

PROCEDURE B:

Preparation of racemic naphythylalanine amide



Naphthalene-1-carboxylic acid is dissolved in dry THF and 5 equiv. of borane dimethylsulfide complex are added. A mixture obtained is stirred at RT, diluted with EtAc, washed with 1N

HCl and 5% $NaHCO_3$ solution, dried and solvent is evaporated. (Naphthalene-1-yl)-methanol is obtained, dissolved in CH_2Cl_2 and 1.5 equiv. of Dess-Martin reagent are added at RT. The mixture obtained is diluted with EtAc, extracted with 1N HCl and 5% $NaHCO_3$-solution, dried and solvent is evaporated. Naphthalene-1-carboxaldehyde is obtained, dissolved with 1 equiv. of racemic-Boc-α-phosphonoglycine trimethylester in CH_2Cl_2 and 1.1 equiv. of DBU are added. The mixture obtained is stirred at RT and washed with 1N HCl and 5% $NaHCO_3$ solution. The phases are separated, the organic phase obtained is dried and solvent is evaporated. Crude 2-benzyloxy-carbonylamino-3-(naphthalene-1-yl)-acrylic acid methyl ester (cis/trans mixture) is obtained and directly used further. 2-Benzyloxycarbonylamino-3-(naphthalene-1-yl)-acrylic acid methyl ester is dissolved in MeOH/H_2O at pH 6.5 (phosphate buffer) and 20 w/w% of 10% Pd/C are added. The mixture obtained is hydrogenated at RT and 50 bar, the catalyst is filtered off, from the filtrate obtained solvent is evaporated and racemic naphythylalanine methylester is obtained, dissolved in methanolic ammonia and stirred. Racemic naphythylalanine amide is obtained after extractive workup.

PROCEDURE C:

The compound of example 22 is reacted with 1.5 equiv. of Boc-beta-alanine, 1.5 equiv. of EDC hydrochloride and 0.5 equiv. of DMAP in DMF at RT. The reaction mixture obtained is diluted with EtAc, the organic phase obtained is washed, dried and solvent is evaporated. The evaporation residue obtained is dissolved in TFA/H_2O at 0°, stirred, diluted with dioxan and solvent is evaporated. A residue obtained is purified by e.g. RP-chromatography to give the compound of example 31 in the form of a trifluoroacetate salt.

PROCEDURE D:

The compound of example 31 is reacted with excess of iodomethan in CH_2Cl_2/K_2CO_3 at RT. Solvent is evaporated, the evaporation residue obtained is dissolved in MeOH/H_2O and worked up by solid-phase extraction (e.g. C-18 cartridge, MeOH/H_2O gradient). The compound of example 32 is obtained.

PROCEDURE E:

The compound of example 27 is prepared analogously to the compound of example 26 by reacting the compound of example 22 with succinic anhydride.

PROCEDURE F:

The compound of example 25 is prepared analogously to the compound of example 22 by reacting the Boc-protected compound of example 25 with TFA/H_2O.

PROCEDURE G:

The compounds of example 17, 30, 36 and 37 are prepared analogously to the compound of example 31 by reaction of the compound of example 25 with Boc-glycine and subsequent deprotection.

PROCEDURE H:

The compound of example 33 is prepared by reacting the compound of example 27 with 2.5 equiv. of NMM and 2 equiv. of EDC-hydrochloride in DMF at 0° for 4 hours at pH 8 (adjustment by addition of TFA). The reaction mixture obtained is diluted with EtAc, the organic phase obtained is washed, dried and solvent is evaporated.

PROCEDURE I:

The compound of example 34 is prepared by reacting a compound of example 27 with 6 equiv. of piperazine and 2 equiv. of EDC-hydrochloride in DMF at pH=8 (adjustment by addition of TFA). A reaction mixture obtained is diluted with EtAc, the organic phase obtained is washed, dried and solvent is evaporated.

Analogously to the procedures as described above, but using appropriate starting materials, compounds of formula I wherein R_1 is methyl and R_2 and R_3 are as defined in TABLE 1 are obtained.

TABLE 1:

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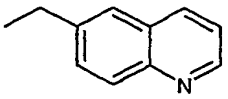
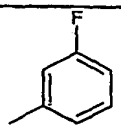
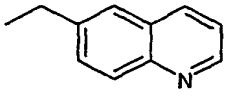
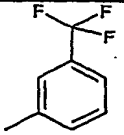
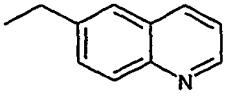
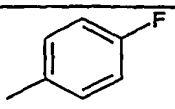
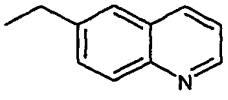
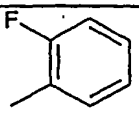
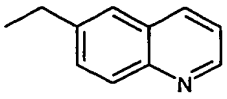
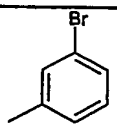
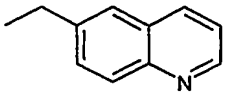
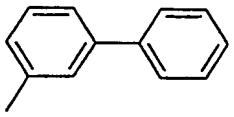
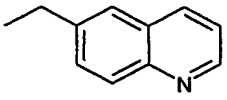
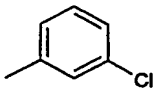
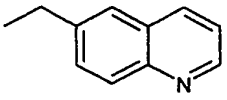
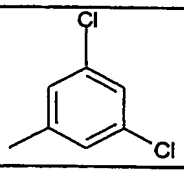
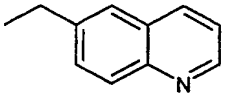
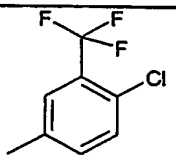
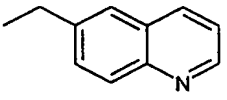
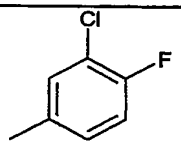
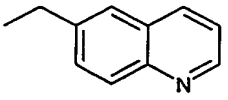
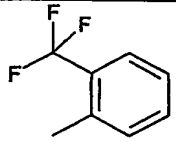
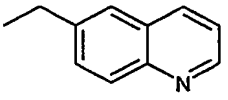
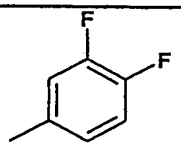
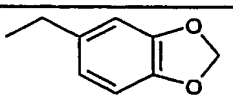
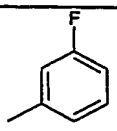
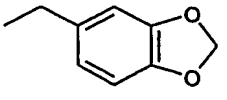
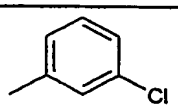
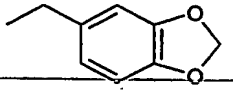
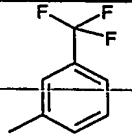
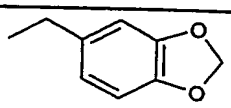
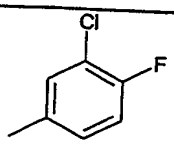
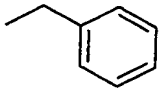
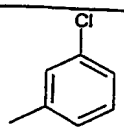
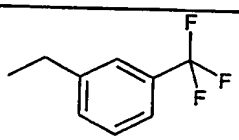
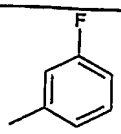
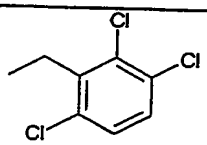
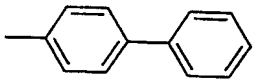
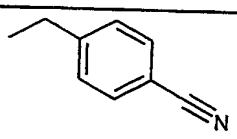
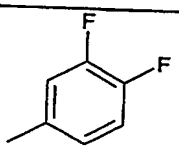
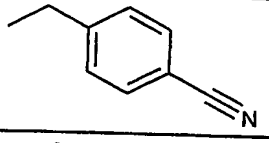
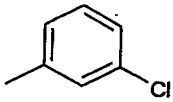
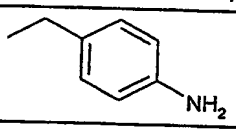
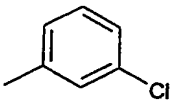
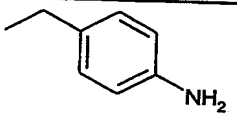
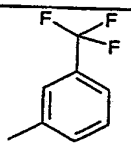
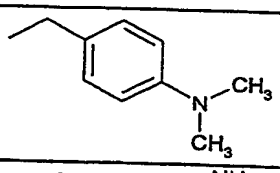
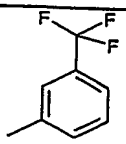
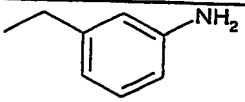
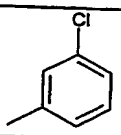
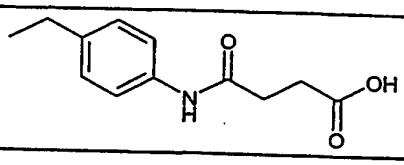
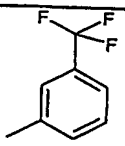
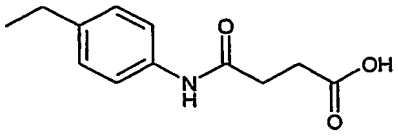
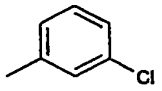
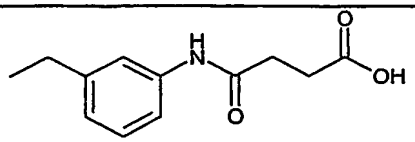
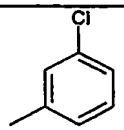
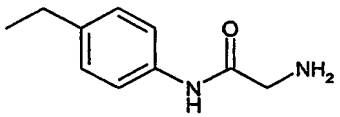
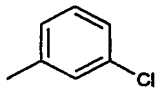
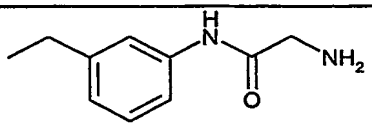
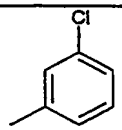
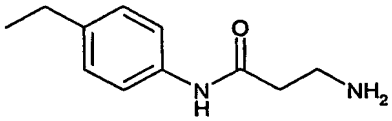
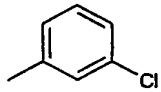
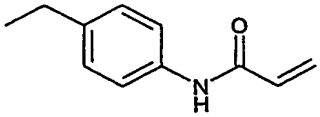
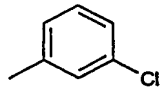
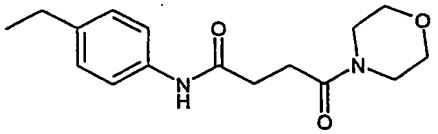
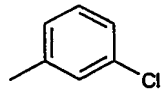
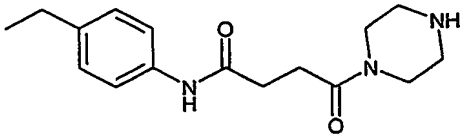
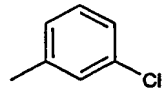
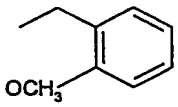
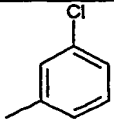
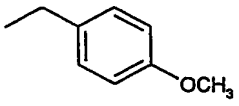
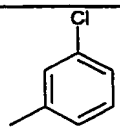
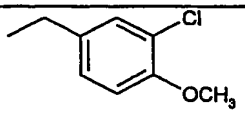
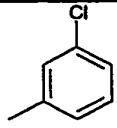
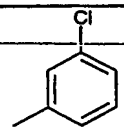
1		
2		
3		
4		

5		
6		
7		
8		
9		
10		
11		
12		
13		
14		
15		

16		
17		
18		
19		
20		
21		
22		
23		
24		
25		
26		

27		
28		
29		
30		
31		
32		
33		
34		
35		
36		
37		
38	-CH_3	

Ex.1-6, 13, 18, 19 and 38 are prepared according to procedure A
Ex. 7-12, 14-16, 20-24, 26, 28, 29 and 35 are prepared according to procedure B
Ex. 31 is prepared according to procedure C
Ex. 32 is prepared according to procedure D
Ex. 27 is prepared according to procedure E
Ex. 25 is prepared according to procedure F
Ex. 17, 30, 36 and 37 are prepared according to procedure G
Ex. 33 is prepared according to procedure H
Ex. 34 is prepared according to procedure I
Compounds of examples 6, 11, 23, 25, 29 and 31 are obtained as trifluoroacetate salts.

EXAMPLE 39: Inhibition of allergic contact dermatitis (ACD) in vivo

a) Method:

Groups of 8 female mice are sensitized epicutaneously with 50 µl 2% oxazolone on the shaved ventral abdomen (day 1) and challenged with 10 µl of 0.2% oxazolone on the inner surface of the right ear (day 8). The unchallenged left ears serve as normal controls and dermatitis is evaluated from the difference in pinnal weight which is taken as a measure of inflammatory swelling (day 9). In addition, activity of myeloperoxidase (MPO) serving as a measure of leukocyte influx in ear homogenates are determined as described by Bradley et al., J.Invest.Dermatol; 78:206-209 (1982). The animals are treated orally 2 hours after challenge with the test compound of example 10. Activity is calculated as the percentage of inhibition of inflammatory auricular swelling and of MPO activity relative to animals treated with the vehicle alone. For comparison mice are treated intraperitoneally with 100 µl monoclonal anti-mouse LFA-1 antibody 1 hour before challenge and evaluated as described.

b) Results:

Oral treatment with a single dose of 0.01-10.0 mg/kg of a compound of example 10 results in an inhibition of the inflammatory response by 40-50%. Inhibition of swelling compared with inhibition of MPO activity is observed. Treatment with 50-200 µg/mouse anti-LFA-1 antibody results in an inhibition by 34-56%.

TABLE 2:

R_f value from Thin Layer Chromatography
[silica gel 60, toluene/i-PrOH 1:1 (=T) or EtAc (=E); unless given otherwise];
^{1}H-NMR (in $CDCl_3$)

Ex. 1: R_f=0.55 (T); 8.84 (dd, 4Hz, 1Hz), 8.82 (dd), 8.11 (d, 9Hz), 8.07 (d, 8Hz), 8.00 (d, 9Hz), 7.97 (d, 9Hz), 7.90 (d, 8Hz), 7.83 (d, 8Hz), 7.76 (d, 8Hz), 7.54 (m), 7.29 (m), 7.20 (dd, 8Hz, 4Hz), 7.06 (d, 8Hz), 6.99 (d, 9Hz), 6.59 (d, 8Hz), 6.54 (s), 6.38 (s br, NH), 6.29 (s br, NH), 6.05 (s), 5.62 (dd, 8Hz, 8Hz), 5.48 (dd, 7Hz, 7Hz), 5.38 (s br, NH), 4.62 (m), 4.00 (d, 15Hz), 3.88 (d, 15Hz), 2.78 (dd, 13Hz, 12Hz), 0.62 (d, 7Hz), 0.59 (d, 7Hz)

Ex. 2: R_f=0.37 (T); 8.81 (dd, 4Hz, 1Hz), 8.01 (d, 9Hz), 7.99 (d, 9Hz), 7.91 (d, 8Hz), 7.04 (d, 8Hz), 6.83 (s), 6.02 (s), 5.70 (dd, 9Hz, 7Hz), 5.49 (dd, 7Hz, 7Hz), 4.60 (m), 4.02 (d, 15Hz), 3.93 (d, 15Hz), 2.87 (dd, 13Hz, 11Hz), 0.57 (d, 7Hz), 0.50 (d, 7Hz)
Ex. 3: R_f=0.65 (T); 8.84 (dd, 4Hz, 2Hz), 8.11 (d, 9Hz), 8.07 (d, 8Hz), 8.00 (d, 9Hz), 7.97 (d, 9Hz), 7.90 (d, 7Hz), 7.83 (d, 8Hz), 7.76 (d, 8Hz), 7.64 (m), 7.55 (m), 7.41 (m), 7.00 (dd, 9Hz, 9Hz), 6.79 (m), 6.54 (s br), 6.30 (s br), 6.04 (s), 5.63 (dd, 8Hz, 8Hz), 5.49 (dd, 7Hz, 7Hz), 5.40 (s br), 4.61 (m), 3.99 (d, 15Hz), 3.87 (d, 15Hz), 2.78 (dd, 13Hz, 11Hz), 0.59 (d, 7Hz), 0.54 (d, 7Hz)
Ex. 4: R_f=0.60 (T); 8.83 (dd, 4Hz, 1Hz), 8.74 (dd, 4Hz, 1Hz), 8.11 (d, 9Hz), 8.02 (d, 9Hz), 7.96 (d, 9Hz), 7.89 (d, 8Hz), 7.81 (d, 8Hz), 7.75 (d, 8Hz), 6.56 (s br), 6.21 (s), 5.55 (dd, 8Hz, 8Hz), 5.52 (dd, 7Hz, 7Hz), 5.42 (s br), 5.38 (s br), 4.62 (m), 3.95 (d, 15Hz), 3.83 (d, 15Hz), 3.55 (dd, 16Hz, 7Hz), 3.45 (dd, 15Hz, 8Hz), 3.30 (dd, 13Hz, 11Hz), 3.19 (dd, 15Hz, 8Hz), 2.81 (dd, 13Hz, 12Hz), 1.84 (ddd, 15Hz, 7Hz, 7Hz), 0.56 (d, 7Hz), 0.54 (d, 7Hz)
Ex. 5: R_f=0.32 (T); 8.84 (dd, 4Hz, 2Hz), 8.15 (d, 8Hz), 8.10 (d, 8Hz), 8.01 (d, 8Hz), 8.00 (d, 8Hz), 7.91 (d, 8Hz), 7.85 (d, 8Hz), 7.77 (d, 8Hz), 7.69 (s), 7.66 (s), 7.63 (dd, 7Hz, 8Hz), 7.55 (dd, 8Hz, 8Hz), 7.42 (m), 7.35 (dd, 4Hz, 8Hz), 7.29 (d, 8Hz), 7.19 (d, 7Hz), 6.99 (dd, 8Hz, 8Hz), 6.78 (s), 6.74 (d, 8Hz), 6.54 (s br), 6.30 (s br), 6.01 (s), 5.63 (dd, 8Hz, 8Hz), 5.48 (dd, 7Hz, 7Hz), 5.43 (s br), 5.35 (s br), 4.62 (m), 4.01 (d, 15Hz), 3.92 (m), 3.89 (d, 16Hz), 3.69 (dd, 15Hz, 8Hz), 3.65 (d, 16Hz), 3.54 (dd, 15Hz, 8Hz), 3.42 (dd, 15Hz, 8Hz), 3.41 (dd, 15Hz, 9Hz), 3.34 (dd, 12Hz, 11Hz), 2.78 (dd, 13Hz, 11Hz), 1.86 (ddd, 15Hz, 6Hz, 6Hz), 0.63 (d, 7Hz), 0.58 (d, 7Hz)
Ex. 6 R_f=0.34 (T 4:1); 9.15 (dd, 5Hz, 1Hz), 9.09 (dd, 5Hz, 1Hz), 8.66 (d, 8Hz), 8.47 (d, 9Hz), 8.42 (d, 9Hz), 8.42 (d, 8Hz), 8.02 (d, 8Hz), 7.98 (d, 9Hz), 7.97 (s), 7.93 (d, 7Hz), 7.91 (s), 7.67 (dd, 12Hz, 1Hz), 7.65 (dd, 13Hz, 1Hz), 7.60 (m), 7.50 (ddd, 8Hz, 8Hz, 3Hz), 6.99 (d, 7Hz), 6.94 (s), 6.91 (s br), 6.62 (s br), 6.57 (s br), 6.18 (s), 5.67 (dd, 7Hz, 7Hz), 5.60 (dd, 7Hz, 7Hz), 4.59 (m), 4.02 (d, 16Hz), 3.94 (d, 17Hz), 3.91 (s), 3.88 (m), 3.74 (dd, 15Hz, 7Hz), 3.53 (dd, 15Hz, 9Hz), 3.39 (dd, 12Hz, 12Hz), 3.03 (dd, 13Hz, 12Hz), 0.69 (d, 7Hz), 0.63 (d, 7Hz)
Ex. 7: R_f=0.45 (T 4:1); 8.84 (m), 8.12 (d, 9Hz), 8.07 (d, 8Hz), 8.00 (d, 9Hz), 7.97 (d, 9Hz), 7.90 (d, 8Hz), 7.83 (d, 8Hz), 7.76 (d, 9Hz), 7.04 (dd, 8Hz, 8Hz), 6.69 (s), 6.68 (s), 6.57 (s br), 6.33 (s br), 5.62 (dd, 8Hz, 8Hz), 5.48 (dd, 7Hz, 7Hz), 4.61 (m), 4.00 (d, 15Hz), 3.92 (m), 3.89 (d, 15Hz), 2.78 (dd, 11Hz, 12Hz), 0.62 (d, 7Hz), 0.58 (d, 7Hz)
Ex. 8: R_f=0.65 (T); 8.84 (dd, 4Hz, 2Hz), 7.98 (d, 9Hz), 7.89 (d, 8Hz), 7.85 (d, 8Hz), 7.76 (d, 8Hz), 7.53 (m), 7.41 (dd, 7Hz, 7Hz), 7.28 (m), 7.17 (s), 7:17 (s), 7.13 (m), 6.53 (s), 6.49 (s br), 6.29 (s br), 5.91 (m), 5.60 (dd, 8Hz, 8Hz), 5.57 (s br), 5.45 (s br), 5.44 (dd, 7Hz, 7Hz), 4.62 (), 4.01 (d, 15Hz), 3.97 (m), 3.90 (d, 16Hz), 3.41 (dd, 15Hz, 7Hz), 2.78 (dd, 13Hz, 11Hz), 1.91 (m), 0.68 (d, 7Hz), 0.62 (d, 7Hz)
Ex. 9: R_f=0.55 (T 4:1); 8.78 (dd, 4Hz, 2Hz), 7.97 (d, 8Hz), 7.88 (d, 9Hz), 7.83 (d, 7Hz), 7.81 (d, 7Hz), 7.69 (d, 9Hz), 7.57 (s), 7.52 (s), 7.47 (dd, 7Hz, 8Hz), 7.23 (d, 7Hz), 7.20 (dd, 8Hz, 4Hz), 7.02 (s), 6.85 (s br), 6.81 (s br), 6.37 (s br), 6.19 (s br), 5.86 (s), 5.66 (dd, 9Hz, 6Hz), 5.48 (dd, 7Hz, 8Hz), 4.54 (m), 4.01 (m), 3.94 (d, 15Hz), 3.88 (d, 15Hz), 3.55 (dd, 15Hz,

7Hz), 3.37 (dd, 15Hz, 9Hz), 2.85 (ddd, 14Hz, 9Hz, 3Hz), 0.62 (d, 7Hz), 0.49 (d, 7Hz)
Ex. 10: R_f=0.30 (T 4:1); 8.89 (d, 4Hz), 8.85 (d, 3Hz), 8.01 (d, 8Hz), 7.99 (d, 8Hz), 7.90 (d, 8Hz), 7.86 (d, 8Hz), 7.77 (d, 8Hz), 6.87 (dd, 8Hz, 8Hz), 6.45 (s br), 6.23 (s br), 5.97 (s br), 5.61 (dd, 8Hz, 8Hz), 5.46 (dd, 7Hz, 7Hz), 5.39 (s), 4.63 (m), 4.00 (d, 15Hz), 3.89 (d, 14Hz), 2.80 (dd, 13Hz, 11Hz), 0.66 (d, 7Hz), 0.59 (d, 7Hz)
Ex. 11: R_f=0.40 (T 4:1); 9.12 (d, 5Hz), 9.08 (d, 4Hz), 8.60 (d, 8Hz), 8.45 (d, 9Hz), 8.40 (d, 9Hz), 8.39 (s), 8.39 (s), 8.37 (d, 10Hz), 8.02 (d, 8Hz), 7.90 (d, 7Hz), 7.87 (s), 7.77 (d, 8Hz), 7.38 (d, 8Hz), 7.18 (d, 8Hz), 6.65 (s br), 6.40 (s br), 6.07 (s), 5.89 (s br), 5.81 (s br), 5.60 (dd, 8Hz, 8Hz), 5.54 (dd, 8Hz, 8Hz), 4.57 (m), 3.98 (d, 16Hz), 3.90 (d, 16Hz), 3.00 (dd, 12Hz, 12Hz), 0.68 (d, 7Hz), 0.58 (d, 7Hz)
Ex. 12: R_f=0.34 (E); 8.85 (dd, 4Hz, 2Hz), 8.12 (d, 8Hz), 8.07 (d, 9Hz), 7.99 (d, 8Hz), 7.98 (d, 9Hz), 7.90 (d, 8Hz), 7.84 (d, 8Hz), 7.77 (d, 8Hz), 7.64 (m), 7.54 (m), 7.42 (dd, 8Hz, 8Hz), 7.28 (d, 7Hz), 7.21 (dd, 8Hz, 4Hz), 7.10 (dd, 9Hz, 9Hz), 6.60 (m), 6.51 (d, 9Hz), 6.43 (s br), 6.33 (s br), 6.20 (s br), 5.99 (s), 5.60 (dd, 8Hz, 8Hz), 5.46 (dd, 7Hz, 8Hz), 5.37 (s br), 4.64 (m), 4.00 (d, 15Hz), 3.89 (d, 15Hz), 3.52 (m), 3.41 (dd, 15Hz, 8Hz), 2.79 (dd, 13Hz, 11Hz), 0.66 (d, 7Hz), 0.60 (d, 7Hz)
Ex. 13: R_f=0.67 (T); 8.01 (d, 8Hz), 7.88 (d, 8Hz), 7.77 (d, 8Hz), 7.59 (ddd, 8Hz, 7Hz, 1Hz), 7.52 (dd, 7Hz, 7Hz), 7.43 (dd, 8Hz, 8Hz), 7.31 (d, 7Hz), 7.27 (s), 7.04 (d, 8Hz), 6.96 (d, 9Hz), 6.75 (d, 8Hz), 6.73 (d, 1Hz), 6.67 (m), 6.52 (d, 8Hz), 6.43 (d, 8Hz), 6.36 (s br, NH), 5.98 (s), 5.84 (d, 1Hz), 5.75 (d, 1Hz), 5.66 (dd, 8Hz, 8Hz), 5.58 (s br, NH), 5.47 (dd, 7Hz, 7Hz), 4.58 (m), 3.89 (m), 3.73 (d, 15Hz), 3.60 (d, 15Hz), 3.35 (d, 15Hz), 3.30 (d, 13Hz), 2.77 (dd, 13Hz, 11Hz), 0.60 (d, 7Hz), 0.56 (d, 7Hz)
Ex. 14: R_f=0.55 (T); R_f=0.67, 8.01 (d, 8Hz), 7.88 (d, 8Hz), 7.78 (d, 8Hz), 6.43 (d, 8Hz), 5.96 (s br), 5.87 (d, 1Hz), 5.84 (d, 1Hz), 5.8 (d, 1Hz), 5.75 (d, 1Hz), 5.66 (dd, ~7.5Hz, ~7.5Hz), 5.45 (dd, ~7.5Hz, ~7.5Hz), 4.58 (ddq, 7Hz, 13Hz), 3.89 (ddq, 7Hz, 12Hz, 6Hz), 2.77 (dd, 14Hz, 11Hz), 0.61 (d, 7Hz), 0.55 (d, 7Hz)
Ex. 15: R_f=0.75 (T); 7.94 (d, 8Hz), 7.80 (d, 8Hz), 7.70 (d, 8Hz), 7.70 (d, 8Hz), 7.51 (ddd, 8Hz, 7Hz, 1Hz), 7.16 (d, 9Hz), 6.77 (s), 6.72 (s), 6.65 (m), 6.45 (d, 8Hz), 6.36 (d, 8Hz), 6.27 (s br), 5.94 (s br), 5.79 (d, 1Hz), 5.76 (d, 1Hz), 5.74 (d, 1Hz), 5.68 (d, 1Hz), 5.63 (dd, 8Hz, 8Hz), 5.58 (s br), 5.44 (s br), 5.41 (dd, 7Hz, 7Hz), 4.50 (m), 3.83 (m), 3.67 (d, 15Hz), 3.53 (d, 15Hz), 3.39 (dd, 15Hz, 7Hz), 3.19 (d, 15Hz), 2.89 (d, 16Hz), 2.72 (dd, 13Hz, 11Hz), 0.46 (d, 7Hz), 0.39 (d, 7Hz)
Ex. 16: R_f=0.53 (E); 8.01 (d, 8Hz), 7.89 (d, 8Hz), 7.78 (d, 8Hz), 7.60 (ddd, 8Hz, 7Hz, 1Hz), 7.53 (ddd, 8Hz, 7Hz, 1Hz), 7.43 (dd, 8Hz, 7Hz), 7.43 (dd, 8Hz, 7Hz), 7.36 (d, 7Hz), 7.31 (d, 8Hz), 7.21 (s), 7.07 (d, 9Hz), 6.97 (dd, 8Hz, 9Hz), 6.53 (dd, 8Hz, 1Hz), 6.45 (s br), 6.45 (d, 8Hz), 6.25 (s br), 5.92 (s), 5.88 (d, 1Hz), 5.85 (d, 1Hz), 5.82 (d, 1Hz), 5.76 (d, 1Hz), 5.65 (dd, 8Hz, 8Hz), 5.43 (dd, 7Hz, 7Hz), 5.36 (s br), 4.59 (m), 3.92 (m), 3.74 (d, 15Hz), 3.61 (d, 15Hz), 3.31 (d, 15Hz), 2.78 (dd, 13Hz, 11Hz), 0.64 (d, 7Hz), 0.57 (d, 7Hz)
Ex. 17: R_f=0.47 (E); 8.00 (d, 8Hz), 7.89 (d, 8Hz), 7.89 (d, 7Hz), 7.79 (d, 8Hz), 7.61 (ddd, 8Hz, 7Hz, 1Hz), 7.54 (ddd, 8Hz, 7Hz, 1Hz), 7.45 (dd, 8Hz, 7Hz), 7.05 (d, 7Hz), 6.66 (s), 6.64 (s), 6.59 (s br), 6.33 (s br), 5.96 (s), 5.62 (dd, 8Hz, 8Hz), 5.55 (s br), 5.48 (s br), 5.45 (dd, 7Hz, 7Hz), 4.59 (m), 3.86 (d, 15Hz), 3.70 (d, 14Hz), 3.58 (dd, 16Hz, 8Hz), 3.42 (dd, 15Hz, 8Hz), 2.62 (dd, 13Hz, 11Hz), 1.80 (ddd, 15Hz, 6Hz, 6Hz), 0.59 (d, 7Hz), 0.54 (d, 7Hz)

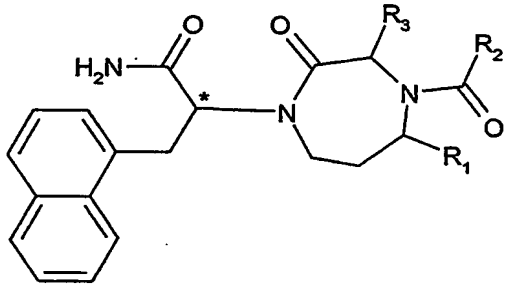
Ex. 18: R_f=0.75 (T); 8.04 (d, 8Hz), 7.89 (d, 8Hz), 7.77 (d, 8Hz), 7.59 (ddd, 8Hz, 7Hz, 1Hz), 7.52 (dd, 8Hz, 7Hz), 7.27 (s), 6.68 (d, 8Hz), 6.60 (s br), 6.56 (d, 8Hz), 6.33 (s br), 5.90 (s), 5.68 (dd, 8Hz, 8Hz), 5.60 (s br), 5.54 (dd, 7Hz, 7Hz), 5.50 (s br), 4.57 (m), 3.80 (m), 3.80 (d, 15Hz), 3.70 (d, 15Hz), 3.30 (dd, 13Hz, 11Hz), 2.83 (dd, 13Hz, 11Hz), 0.59 (d, 7Hz), 0.58 (d, 7Hz)
Ex. 19: R_f=0.47 (T); δ = 8.07 (d, 8.5Hz), 8.01 (d, 8.5Hz), 7.86 (d, 8Hz), 7.78 (d, 8Hz), 7.74 (d, 8Hz), 7.55 (d, 8Hz), 6.68 (s, br), 6.34 (s, br), 6.28 (s), 5.63 (dd, 5.5Hz, 9Hz), 5.55 (dd, 8Hz, 8Hz), 5.48 (s, br), 4.64 (m), 4.41 (d, 16.5Hz), 4.14 (d, 16.5Hz), 4.02 (d, 16.5Hz), 3.97 (m), 3.68 (dd, 8.5Hz, 8.5Hz), 3.32 (dd, 11Hz, 14Hz), 0.79 (d, 7Hz), 0.70 (d, 7Hz)
Ex. 20: R_f=0.55 (E); 8.05 (d, 8Hz), 7.93 (d, 8Hz), 7.79 (d, 8Hz), 7.63 (ddd, 8Hz, 7Hz, 1Hz), 7.44 (dd, 8Hz, 8Hz), 7.20 (s), 7.18 (d, 8Hz), 7.06 (d, 8Hz), 6.52 (s br), 5.79 (s), 5.63 (dd, 9Hz, 6Hz), 5.45 (s br), 4.56 (m), 3.78 (d, 15Hz), 3.66 (d, 15Hz), 2.70 (dd, 14Hz, 11Hz), 0.64 (d, 7Hz), 0.60 (d, 7Hz)
Ex. 21: R_f=0.55 (T 4:1); 7.98 (d, 8Hz), 7.95 (d, 8Hz), 7.84 (d, 7Hz), 7.81 (d, 9Hz), 7.71 (d, 8Hz), 7.35 (dd, 8Hz, 8Hz), 7.24 (d, 8Hz), 7.16 (s), 7.08 (d, 8Hz), 6.98 (d, 8Hz), 6.69 (d br, 8Hz), 6.66 (s), 6.59 (s br), 6.28 (s br), 5.73 (s), 5.61 (dd, 8Hz, 7Hz), 5.58 (dd, 9Hz, 6Hz), 5.52 (s br), 4.45 (m), 3.70 (d, 15Hz), 3.62 (m), 3.58 (d, 15Hz), 3.41 (d, 15Hz), 3.22 (dd, 12Hz, 12Hz), 2.61 (dd, 13Hz, 11Hz), 1.98 (s), 1.79 (s), 0.53 (d, 7Hz), 0.49 (d, 7Hz)
Ex. 22: R_f=0.40 (T 4:1); 7.96 (d, 9Hz), 7.95 (d, 8Hz), 7.84 (d, 8Hz), 7.80 (d, 8Hz), 7.72 (d, 8Hz), 7.48 (d, 7Hz), 7.40 (dd, 8Hz, 8Hz), 7.22 (d, 7Hz), 6.98 (d, 8Hz), 6.73 (d, 8Hz), 6.11 (d, 8Hz), 5.92 (s), 5.52 (dd, 7Hz, 6Hz), 5.42 (s br), 4.50 (m), 3.79 (m), 3.65 (d, 15Hz), 3.49 (d, 14Hz), 3.41 (dd, 8Hz, 16Hz), 2.52 (dd, 12Hz, 12Hz), 0.51 (d, 7Hz), 0.45 (d, 7Hz)
Ex. 23: R_f=0.57 (T); 7.99 (d, 8Hz), 7.97 (d, 8Hz), 7.84 (d, 8Hz), 7.73 (d, 8Hz), 7.54 (ddd, 8Hz, 7Hz, 1Hz), 7.45 (s), 6.97 (d, 8Hz), 6.75 (d, 8Hz), 6.59 (d, 8Hz), 6.17 (d, 8Hz), 5.96 (s), 5.76 (s br), 5.61 (dd, 8Hz, 7Hz), 5.46 (dd, 7Hz, 7Hz), 4.50 (m), 3.83 (m), 3.67 (d, 15Hz), 3.51 (d, 15Hz), 2.56 (dd, 13Hz, 10Hz), 0.45 (d, 7Hz), 0.39 (d, 7Hz)
Ex. 24: R_f=0.53 (T 4:1); 7.97 (d, 8Hz), 7.84 (d, 7Hz), 7.74 (d, 8Hz), 7.31 (s), 7.24 (d, 7Hz), 7.06 (d, 9Hz), 6.80 (d, 8Hz), 6.73 (s), 6.59 (d, 9Hz), 6.53 (s br), 6.16 (d, 9Hz), 6.05 (s), 5.61 (dd, 8Hz, 8Hz), 5.46 (dd, 7Hz, 7Hz), 5.33 (s br), 5.27 (s br), 4.55 (m), 3.85 (m), 3.73 (d, 15Hz), 3.53 (d, 15Hz), 3.22 (d, 15Hz), 2.73 (s), 2.58 (s), 0.45 (d, 7Hz), 0.38 (d, 7Hz)
Ex. 25: R_f=0.65 (T; free base); 7.98 (d, 8Hz), 7.85 (d, 7Hz), 7.77 (d, 8Hz), 7.75 (d, 8Hz), 7.18 (m), 6.58 (s br), 6.31 (s br), 6.00 (s), 5.35 (m), 4.93 (m), 4.45 (m), 3.44 (d, 15Hz), 3.22 (dd, 13Hz, 11Hz), 0.58 (d, 7Hz), 0.50 (d, 7Hz)
Ex. 26: R_f=0.31 (T) tailing; 9.00 (s), 8.79 (s), 7.97 (d, 9Hz), 7.83 (d, 8Hz), 7.72 (d, 8Hz), 7.15 (s), 7.10 (d, 8Hz), 7.02 (d, 8Hz), 6.86 (s), 6.65 (s br), 6.16 (s br), 6.00 (s br), 5.89 (s), 5.64 (dd, 8Hz, 8Hz), 5.41 (dd, 7Hz, 7Hz), 4.50 (m), 3.86 (m), 3.72 (d, 15Hz), 3.62 (d, 15Hz), 3.26 (d, 15Hz), 2.70 (dd, 13Hz, 11Hz), 2.53 (m), 1.82 (m), 0.46 (d, 7Hz), 0.39 (d, 7Hz)
Ex. 27: R_f=0.30 (T); 8.15 (d, 9Hz), 8.09 (d, 8Hz), 7.91 (d, 8Hz), 7.91 (d, 8Hz), 7.80 (d, 8Hz), 7.52 (m), 7.40 (dd, 8Hz, 7Hz), 7.36 (d, 8Hz), 7.13 (d, 8Hz), 6.95 (s), 6.85 (d, 8Hz), 6.65 (s), 5.82 (s), 5.79 (dd, 10Hz, 6Hz), 5.59 (dd, 10Hz, 6Hz), 4.47 (m), 4.05 (m), 3.76 (m), 3.48 (dd, 14Hz, 10Hz), 2.92 (dd, 14Hz, 11Hz), 2.62 (m), 2.51 (m), 0.54 (d, 7Hz), 0.46 (d, 7Hz)

Ex. 28: R_f=0.65 (T; free base); 8.42 (s), 8.37 (s), 7.98 (d, 8Hz), 7.84 (d, 8Hz), 7.74 (d, 8Hz), 7.55 (dd, 7Hz, 7Hz), 7.40 (d, 8Hz), 7.35 (d, 7Hz), 7.13 (s), 6.82 (s), 6.80 (s), 6.67 (s br), 6.29 (s br), 5.96 (s), 5.37 (s br), 4.99 (s br), 4.48 (m), 3.78 (d, 15Hz), 3.22 (dd, 12Hz, 13Hz), 0.57 (d, 7Hz), 0.49 (d, 7Hz)
Ex. 29: R_f=0.45 (RP-8, MeOH/H_2O/TFA 70:30:1); 8.18 (d, 9Hz), 8.09 (d, 8Hz), 7.91 (d, 8Hz), 7.90 (d, 8Hz), 7.79 (d, 8Hz), 7.49 (d, 8Hz), 7.38 (dd, 8Hz, 8Hz), 6.93 (s), 6.88 (s), 6.87 (d, 8Hz), 6.59 (s), 5.81 (dd, 10Hz, 6Hz), 5.78 (s), 5.56 (dd, 10Hz, 6Hz), 4.44 (m), 4.07 (m), 3.81 (s), 3.77 (s), 3.72 (s), 3.23 (dd, 13Hz, 11Hz), 3.01 (dd, 14Hz, 10Hz), 0.52 (d, 7Hz), 0.44 (d, 7Hz)
Ex. 30: 9.84 (s br), 9.79 (s br), 7.98 (d, 8Hz), 7.84 (d, 8Hz), 7.74 (d, 8Hz), 7.53 (dd, 7Hz, 7Hz), 7.47 (dd, 7Hz, 8Hz), 7.40 (d, 7Hz), 7.25 (s), 6.95 (dd, 7Hz, 8Hz), 6.80 (d, 8Hz), 6.74 (s br), 6.24 (s br), 5.95 (s), 5.44 (s br), 4.96 (s br), 4.44 (m), 3.19 (dd, 13Hz, 12Hz), 2.73 (dd, 11Hz, 11Hz), 0.54 (d, 7Hz), 0.48 (d, 7Hz)
Ex. 31: R_f=0.52 (BuOH/MeOH/H_2O/AcOH 10:5:2:1); 8.16 (d, 8Hz), 8.09 (d, 9Hz), 7.91 (d, 8Hz), 7.80 (d, 8Hz), 7.60 (d, 9Hz), 7.57 (ddd, 8Hz, 7Hz, 1Hz), 7.46 (m), 7.40 (dd, 8Hz, 7Hz), 7.29 (s), 7.18 (d, 8Hz), 6.94 (s), 6.89 (d, 8Hz), 6.63 (s), 5.81 (s), 5.79 (dd, 10Hz, 6Hz), 5.57 (dd, 10Hz, 6Hz), 4.46 (m), 4.08 (m), 3.78 (s), 3.70 (dd, 15Hz, 6Hz), 3.58 (m), 3.48 (dd, 15Hz, 10Hz), 3.23 (dd, 6Hz, 6Hz), 3.11 (dd, 13Hz, 7Hz), 2.99 (dd, 13Hz, 11Hz), 2.75 (dd, 6Hz, 6Hz), 2.62 (dd, 13Hz, 7Hz), 0.53 (d, 7Hz), 0.45 (d, 7Hz)
Ex. 32: R_f=0.65 (T); 8.04 (m br), 7.94 (d, 7Hz), 7.81 (d, 8Hz), 6.73 (s), 6.62 (s br), 6.36 (d, 16Hz), 6.30 (d, 17Hz), 5.96 (s), 5.73 (d, 8Hz), 5.65 (d, 9Hz), 5.55 (m Br), 4.57 (m), 0.59 (d), 0.55 (d, 6Hz)
Ex. 33: R_f=0.42 (T); 8.04 (d, 8Hz), 8.00 (d, 9Hz), 7.93 (d, 8Hz), 7.88 (d, 8Hz), 7.80 (d, 8Hz), 7.76 (s), 7.07 (d, 8Hz), 6.98 (d, 8Hz), 6.94 (s), 6.66 (s), 6.62 (s br), 5.96 (s), 5.59 (dd, 8Hz, 8Hz), 5.51 (dd, 7Hz, 7Hz), 4.58 (m), 3.83 (m), 3.76 (d, 15Hz), 3.64 (m), 3.58 (m), 3.47 (m), 2.62 (m), 0.58 (d, 7Hz), 0.54 (d, 7Hz)
Ex. 34: R_f=0.37 (RP-8 MeOH/H_2O/TFA 70:30:12); 9.90 (s br), 8.22 (d, 8Hz), 8.18 (d, 8Hz), 7.95 (d, 8Hz), 7.82 (d, 8Hz), 7.51 (d, 8Hz), 7.34 (m), 7.25 (s), 7.11 (d, 8Hz), 7.02 (d, 9Hz), 6.69 (s), 5.60 (dd, 10Hz, 5Hz), 5.45 (dd, 10Hz, 5Hz), 4.35 (m), 4.14 (dd, 5Hz, 5Hz), 4.06 (m), 3.76 (d, 16Hz), 3.70 (d, 15Hz), 0.48 (d, 6Hz), 0.39 (d, 7Hz)
Ex. 35: R_f=0.42 (E), 8.04 (d, 9Hz), 7.89 (d, 8Hz), 7.77 (d, 8Hz), 7.59 (ddd, 8Hz, 7Hz, 1Hz), 7.52 (ddd, 8Hz, 7Hz, 1Hz), 7.42 (dd, 8Hz, 7Hz), 6.84 (d, 8Hz), 6.66 (dd, 7Hz, 7Hz), 6.60 (s br), 6.34 (s br), 6.13 (s), 5.59 (dd, 8Hz, 8Hz), 5.44 (dd, 7Hz, 7Hz), 5.37 (s br), 4.59 (m), 3.88 (m), 3.80 (s), 3.74 (s), 3.72 (d, 6Hz), 3.42 (dd, 15Hz, 8Hz), 3.31 (ddd, 13Hz, 10Hz, 2Hz), 2.92 (dd, 13Hz, 11Hz), 0.63 (d, 7Hz), 0.53 (d, 7Hz)
Ex. 36: R_f=0.44 (E); 7.97 (d, 9Hz), 7.83 (d, 9Hz), 7.73 (d, 8Hz), 7.52 (dd, 8Hz, 8Hz), 7.35 (dd, 7Hz, 7Hz), 6.83 (d, 9Hz), 6.62 (d, 8Hz), 6.58 (s br), 6.49 (s), 6.32 (d, 9Hz), 5.89 (s), 5.57 (dd, 8Hz, 7Hz), 5.47 (dd, 7Hz, 7Hz), 5.41 (s br), 4.51 (m), 3.71 (s), 3.60 (s), 3.56 (d, 9Hz), 3.38 (s), 2.53 (dd, 13Hz, 11Hz), 1.71 (ddd, 15Hz, 6Hz, 6Hz), 0.51 (d, 7Hz), 0.46 (d, 7Hz)

Ex. 37: R_f=0.37 (E); 8.06 (d, 8Hz), 8.01 (d, 8Hz), 7.90 (d, 8Hz), 7.81 (d, 8Hz), 7.59 (dd, 7Hz, 7Hz), 7.52 (dd, 8Hz, 8Hz), 7.48 (dd, 8Hz, 8Hz), 7.16 (s), 6.86 (dd, 8Hz, 7Hz), 6.80 (d, 8Hz), 6.71 (s), 6.69 (dd, 8Hz, 2Hz), 6.65 (s br), 6.36 (s br), 6.07 (d, 8Hz), 5.91 (s), 5.66 (dd, 8Hz, 8Hz), 5.60 (dd, 7Hz, 7Hz), 5.51 (s br), 4.57 (m), 3.76 (s), 3.73 (d, 15Hz), 3.52 (s), 2.69 (dd, 13Hz, 11Hz), 0.60 (d, 7Hz), 0.57 (d, 7Hz)
Ex. 38: R_f=0.46 (toluene/i-PrOH 4:1) 8.07 (d, 8Hz), 8.00 (d, 8Hz), 7.87 (dd, 8Hz, 2Hz), 7.76 (d, 8Hz), 7.57 (ddd, 8Hz, 7Hz, 1.5Hz), 7.50 (ddd, 8Hz, 7Hz, 1Hz), 7.43 (dd, 7Hz, 7Hz), 7.23 (m), 6.68 (s br,), 6.42 (s br), 5.79 (s), 5.70 (dd, 10Hz, 6Hz), 5.61 (s, br), 5.52 (dd, 8Hz, 8Hz), 4.55 (m), 3.68 (m), 3.34 (dd), 3.10 (dd, 13.5Hz, 11Hz), 2.09 (s), 0.64 (d, 7Hz), 0.59 (d, 7Hz)

Patent claims

1. A compound of formula



I

wherein

R_1 is (C_{1-4})alkyl,

R_2 is (C_{1-4})alkyl or $-(CH_2)_n-R_4$, wherein

n is 1, 2, 3 or 4 and

R_4 is unsubstituted or substituted

- phenyl or
- phenyl anellated with another ring system, which other ring system is a 5- or 6-membered heterocycle, having one to 4 heteroatoms selected from N, O or S, e.g. wherein substituents are selected from the group consisting of
  - halogen,
  - unsubstituted amino or amino substituted by one or two (C_{1-4})alkyl,
  - cyano,
  - (C_{1-4})alkoxy,
  - (C_{1-6})haloalkyl and

R_3 is substituted phenyl, e.g. one or morefold, wherein the substituents are selected from the group consisting of

- halogen,
- (C_{1-6})haloalkyl,
- unsubstituted or substituted phenyl, wherein substitutents are as indicated under "substituted phenyls" in the meaning of R_4.

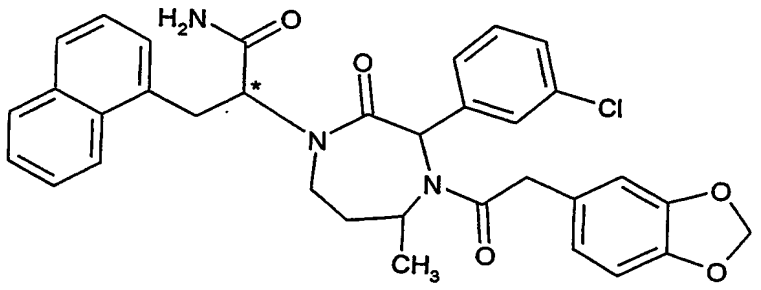
2. A compound of claim 1 wherein

- R_1 is methyl,
- R_2 is methyl or $-CH_2-R_4$ wherein R_4 is benzo(1,3)dioxo-4-yl, benzo(1,3)dioxo-5-yl, quinolin-5-yl, quinolin-6-yl, quinolin-7-yl, quinolin-8-yl, preferably R_4 is benzo(1,3)dioxo-5-yl,

quinolin-6-yl, or phenyl substituted by
one or more
- halogen,
- unsubstituted or substituted amino, wherein substituents are selected from (C_{1-4})alkyl, carboxy(C_{1-4})alkylcarbonyl, amino(C_{1-4})alkylcarbonyl, (C_{1-})alkoxycarbonyl, (C_{2-4})alkylenecarbonyl,
- cyano,
- (C_{1-4})alkoxy,
- (C_{1-6})haloalkyl and

- R_3 is substituted phenyl, wherein the substituents are selected from the group consisting of
- halogen,
- (C_{1-6})haloalkyl and
- unsubstituted phenyl.

3. A compound of claim 1or 2 of formula



I_{PREF}

4. A compound of any one of claims 1 to 3 in the form of a salt.

5. A compound of formula I according to any one of claim 1 to 4 for use as a pharmaceutical.

6. A pharmaceutical composition comprising a compound of formula I according to any one of claim 1 to 5 in association with a pharmaceutically acceptable excipient.

7. A pharmaceutical composition according to claim 6 comprising at least a second drug substance selected from the group consisting of immunosuppressant, immunomodulatory and anti-inflammatory drug.

8. A method for preventing or treating disorders or diseases mediated by LFA-1/ICAM-1, LFA-1/ICAM-2 or LFA-1/ICAM-3 interactions in a subject in need of such treatment, which method comprises administering to said subject an effective amount of a compound of formula I according to any one of claims 1 to 5.

9. Use of a compound of formula I in combination with at least a second drug for applying concomitantly or in sequence in a method according to claim 8.

IL/10-Oct-2003

Abstract

Pharmaceutically active diazepanes, e.g. useful for treating disorders or diseases mediated by LFA-1/ICAM-1, LFA-1/ICAM-2 or LFA-1/ICAM-3 interactions.

PCT/EP2004/000514